REMARKS

Claims 27, 28, and 30-32 are pending. No new matter has been added by way of the above amendments. For instance, claim 27 has been amened to replace "providing" with "producing." Also, claim 28 has been amended to recite that the first and second fusion proteins are encoded by nucleic acids. This amendment to claim 28 was considered a "new issue" by the Examiner and thus Applicants have filed the present Request for Continued Examination. Thus, no new matter has been added. However, since the Examiner previously considered the amendment to claim 28 to raise a new issue (claim 28 being the only claim amendment made in the October 16, 2003 Amendment, which was not entered), Applicants submit that in the event the application is not placed into condition for allowance, the Examiner must enter a non-Final Office Action.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Issues under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claim 27 for reciting "providing" asserting that the specification recites "producing." To expedite prosecution, Applicants have amended the claim language to recite, "producing." Accordingly, this rejection is moot.

Issues under 35 USC § 112, second paragraph

The Examiner has rejected claims 27, 28 and 30-32 under 35 USC § 112, second paragraph for the reasons recited at pages 3-4 of the Office Action. Applicants respectfully traverse this rejection.

The Examiner continues to assert that claim 28 does not further limit claim 27 since the base claim does not recite a nucleic acid. Applicants continue to disagree with the Examiner. Claim 27 simply requires providing a first and a second fusion protein. Claim 28 requires that these fusion proteins be encoded by a nucleic acid that is transfected or transformed into a host cell and expressed. Thus, claim 28 is narrower in scope than claim 27. Regardless, in an effort to further prosecution, Applicants have amended claim 28 to recite that the fusion proteins are encoded by nucleic acids. Thus, this rejection is moot. Reconsideration and withdrawal thereof are requested.

Issues under 35 USC § 103(a)

The Examiner has rejected claims 27, 28 and 30-32 under 35 USC § 103(a) as being obvious over Mayer, US 2002/0037999 (hereinafter referred to as Mayer) in view of Anderson et al., USP 6,180,343 (hereinafter referred to as Anderson) or Katz et al., Biotechniques (hereinafter referred to as Katz). Applicants respectfully traverse this rejection.

Mayer discloses two fusions proteins. The first fusion protein comprises a known protein fused to a coiled-coil heterodimerization domain and the second fusion protein comprises a second protein fused to a coiled-coil heterodimerization domain. Mayer also discloses that the coiled-coil heterodimerization segments may be synthesized *in vitro* and coupled to various chemical groups such as fluorophores (see paragraph [0023]). The secondary reference of Anderson discloses that it is possible to insert small amino acid sequences into GFP without loosing fluorescence. Lastly, the reference of Katz discloses the usefulness of GFP as a cellular marker.

Based upon the above, the Examiner has asserted that it would have been obvious to replace the proteins of Mayer with the GFP of Anderson or Katz. However, the Examiner's rejection is improper since it is missing elements of the claims. For instance, the Examiner's rejection is missing the following:

- the first fusion protein of the claimed invention must comprise a first GFP fragment;
- the second fusion protein of the claimed invention must comprise a second GFP fragment;
- the two GFP fragments must be dissected between amino acid residues of a surface loop; and
- the aim of the method is to identify protein-protein interactions, thus the result of the method is the

presence of fluorescence indicating an interaction between the two fusion proteins.

Thus, the Examiner's rejection lacks elements of the claims. Therefore, even if all of the cited references were hypothetically combined as asserted by the Examiner, one skilled in the art would not arrive at the presently claimed subject matter. Moreover, even if all elements of the present claims were present, a point not conceded by Applicants, there still exists no motivation to combine the references.

Further to the lack of motivation, Applicants point out that Mayer fails to suggest or disclose GFP, but only states that the fusions proteins of the Mayer invention can be coupled to fluorophores to visualize certain events *in vitro*. Importantly, Mayer discloses nothing about placing one portion of GFP on one fusion protein and the other portion of GFP on the other fusion protein. Katz simply discloses that GFP is used as a cellular marker. Consequently, the only reference discussing the structure of GFP is Anderson. Importantly, Anderson discloses that local distortions in the GFP structure are to be avoided. In fact, Anderson fears that this can destabilize folding intermediates or allow access to GFP's buried tripeptide fluorophore and subsequently decrease or even eliminate GFP's fluorescence (see Anderson, column 16, lines 17-26). Anderson never suggest that

separate portions of GFP should be placed in separate fusion proteins.

The Examiner asserts that there appears to be no distinction between Anderson and the present invention (see page 5, second full paragraph of the outstanding Office Action). This is incorrect. Anderson expresses one protein in the cell. This protein (e.g. GFP) is modified to have inserted into the amino acid sequence a peptide sequence. Thus, the expressed protein is not dissected as such, the loop has just been elongated (refer to the abstract of Anderson), as the peptide is fused to an internal structure of GFP (see column 16, lines 18-26 of Anderson). In contrast, the present invention expresses two nucleic acid sequences. The first nucleic acid sequence codes for a full protein fused to only a portion of the amino acids of GFP. The second nucleic acid sequence codes for a full protein fused to the other portion of the amino acids of GFP. The two fusion proteins are expressed individually in the cell. Only when the two full fusion proteins interact, will the two halves of GFP be brought so close together, that the split GFP is correctly folded, oxidized and fluoresce (see paragraph 38, page 13 of the present application).

Accordingly, Anderson fails to disclose the type of GFP structures currently being claimed. In fact, there is no motivation in Anderson to make the modifications to the GFP molecule as presently claimed. In fact, to modify the molecule of

Anderson by placing it in a system such as that disclosed by Mayer would render both references unsuited for their intended purposes. Mayer fails to disclose GFP while Anderson discloses a structurally different GFP.

One of skill in the art looking to solve the problems disclosed by the prior art references would not modify the references as suggested by the Examiner since this would destroy the teachings of the references. Where the Examiner's proposed modification would render the prior art version unsatisfactory for its intended purpose, the proposed combination is improper. In re Gordon, 733 F.2d 980, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); see also Ex parte Rosenfeld, 130 USPQ 113 (POBA 1961). Accordingly, the Examiner's rejection is improper for lack of motivation.

Moreover, the Examiner has failed to establish that there would be a reasonable expectation of success. Based on the forgoing detailed review of Anderson, Applicants submit that a person skilled in the art, upon reading Anderson, would not expect a total dissection of the GFP molecule to function. Rather, it is unreasonable to assert that one skilled in the art, upon reading Anderson, would contemplate that a total dissection of the GFP molecule could result in correct folding and fluorescence, when Anderson so explicitly wants to avoid any distortions in the GFP

structure. Thus, the proposed modification of Mayer would not have a reasonable expectation of success to one of skill in the art.

In summary, Applicants submit that when the references are taken in combination, the Examiner has failed to present a valid prima facie case of obviousness. Reconsideration and withdrawal of this rejection are requested.

In view of the above remarks, Applicants respectfully submit that the present claims define subject matter that is patentable over the cited art and fully complies with the requirements of 35 USC § 112, first and second paragraph. Accordingly, the Examiner is respectfully requested to withdraw all rejections and allow the currently pending claims.

Request for Initialled PTO Form-1449

Applicants filed an Information Disclosure Statement (IDS) on March 27, 2003, with a Form PTO-1449 attached thereto. However, the Examiner has not yet returned an initialled copy of this Form PTO-1449 indicating that the reference listed thereon has been considered. Accordingly, the Examiner is hereby requested to return such initialled copy of the Form PTO-1449 that accompanied the March 27, 2003 IDS.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully

requested to contact Craig A. McRobbie (Reg. No. 42,874) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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